Inactive Ingredients in Medications and Adverse Events
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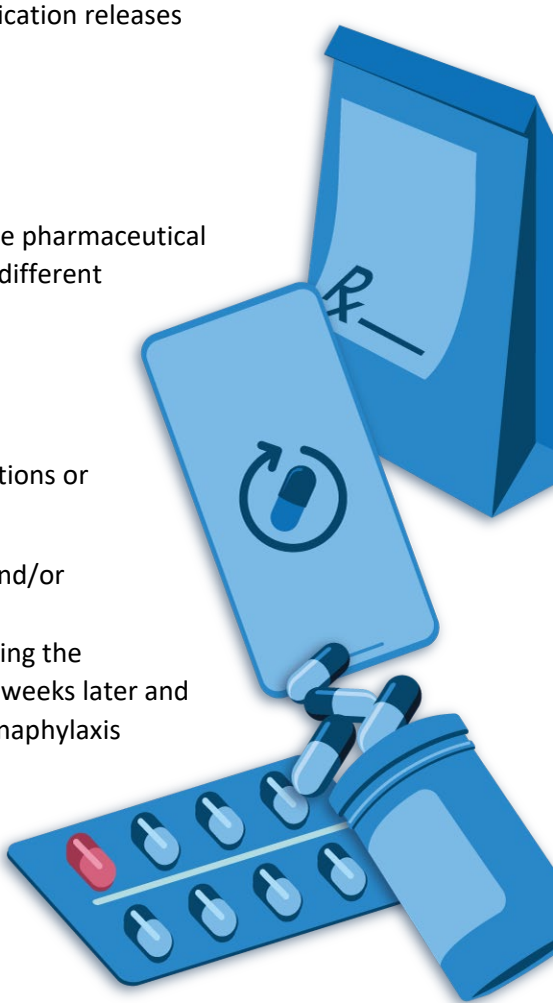
Oral medications contain active ingredient(s) and a mixture of inactive ingredients, called excipients. An active ingredient is defined as a product intended to provide the desired pharmaceutical effect, essentially the product's name (e.g., aspirin is the active ingredient in aspirin). Inactive ingredients are those other than the active ingredient and not intended or expected to produce a biological or therapeutic effect.[1] They are components added during the manufacturing process and include:[2]

- Fillers to increase the bulk of the powder used to make tablets or capsules
- Coatings, film or enteric, to ease swallowing or delay breakdown in the body
- Binders to hold tablets together to control how fast or slow a medication releases
- Dyes to add color
- Flavoring agents to improve taste
- Preservatives to prevent microbial growth
- Other products to facilitate absorption or improve stability

Together the active ingredient(s) and inactive ingredients make up a unique pharmaceutical formulation.[1] It is important to recognize that inactive ingredients may be different between brand and generic versions of the same medication and between different generics.



ADVERSE EVENTS

Inactive ingredients may trigger adverse events in the form of allergic reactions or intolerances:

- An allergy is an immune-mediated response to a pharmaceutical and/or excipient in a sensitized person[1]
    - Allergy symptoms most often occur within one hour of taking the medication, but some reactions may occur hours, days, or weeks later and may include skin rash, hives, itching, fever, swelling, and anaphylaxis
    - Allergies to inactive ingredients in medication are rare[2]

- Drug intolerance is an unpredictable, non-immune reaction defined as an inability to tolerate the adverse effects of a medication, generally at therapeutic or subtherapeutic doses[3]
    - Intolerance is one of several non-immune mediated drug reactions that include side effects, drug toxicity, drug-drug interactions, and overdose[3]
    - Intolerance potentially affects a much larger population with more benign symptoms compared to allergic reactions[1]
    - Intolerance may affect patients' well-being and adherence to drug regimens if the inactive ingredient(s) is/are present in sufficient quantities to trigger a reaction[1]

The inactive ingredients listed below have been cited in the literature as producing adverse events after oral ingestion. This listing is not comprehensive of all inactive ingredients associated with adverse events rather represents ingredients present in > 10% of all solid oral dosage forms according to Reker D, et al, 2019.[1]

- Lactose (food)
- Corn starch (food)
- Polyethylene glycol (PEG) (polymer)
- Povidone (polymer)
- Carboxymethylcellulose (other)
- Gelatin (food)
- Brilliant blue (dye)
- Sunset yellow FCF (dye)
- Allura red (dye)
- Propylene glycol (other)
- Indigo carmine (dye)

COMMON INACTIVE INGREDIENT INQUIRIES MANAGED BY HOSPICE PHARMACISTS

Lactose

- Lactose intolerance is a clinical syndrome in which ingestion of lactose or lactose-containing food causes symptoms (abdominal pain, bloating, flatulence, nausea, diarrhea)[4]
- Lactose malabsorption is a failure of the small bowel to absorb ingested lactose due to lactase deficiency [4] (lactase is the enzyme responsible for breaking down lactose)
- Lactose-containing medications do not need to be avoided in patients with lactose intolerance and/or lactose malabsorption[4]
    - The amount of lactose in tablets is so small that there is no reason to assume that this would result in symptoms
    - Consider looking for lactose in medications only for patients who continue to have symptoms, despite a strict lactose-free diet
    - Advertisements promoting "lactose-free drugs" lack a scientific basis regarding abdominal symptoms and may serve to promote misunderstanding about the dose-effect relationship between lactose dose and development of symptoms

Gluten

- Gluten is a protein found in wheat, barley, and rye[5]
- People may avoid gluten because of a wheat allergy, gluten intolerance, celiac disease, or other reasons (e.g., weight loss, boost mood or energy) [5]
    - Gluten intolerance involves the digestive system – when ingested, gluten may produce abdominal pain, diarrhea, and/or gas in affected patients
    - "Gluten allergy" does not exist however patients with a wheat allergy should avoid foods and topical products containing wheat that trigger symptoms. It is not necessary to avoid gluten from other sources (e.g., barley, rye).
    - Celiac disease is an autoimmune disorder. Gluten ingestion leads to symptoms like gluten intolerance in these patients, but more importantly can lead to malabsorption and damage to the small intestine. A lifelong, gluten-free diet is the primary treatment for patients with celiac disease.
- Most medications do not contain gluten – they usually contain gluten-free starches (e.g., corn, potato, rice, tapioca) [5]
    - Consider looking for gluten in medications only for patients who continue to have symptoms, despite a strict gluten-free diet
    - You won't find the word "gluten" in the medication's product information - sources of gluten in oral medications may include flour, caramel coloring, dextrins, dextrates, dextrimaltose, or other starches (e.g., modified, pregelatinized, sodium starch glycolate).
    - If the source of the starch is wheat, the product may contain gluten. Medications don't contain starches from barley or rye.

Dyes

- Dyes in medications can trigger reactions such as itching, rashes, and anaphylaxis[6]
- Common culprits include FD&C Yellow #5 (tartrazine), Yellow #6, Red #40, Blue #1, and Blue #2[6]
- Note that white medications may not be dye-free[6]
    - Some contain FD&C Blue #1 as a brightener
    - Some antibiotic powders for reconstitution may contain FD&C Red #40 to make the suspension pink
- If a product must be avoided, help find alternatives, such as a different manufacturer or dosage form[6]

ADVERSE EVENT PREVENTION

Take a thorough drug allergy and drug intolerance history

The drug allergy section of the medication profile often lacks details. Lack of related details may lead to unnecessary avoidance of the offending or related drugs. Only 5% to 10% of adverse drug reactions are allergic. With a detailed history, non-allergic reactions could be minimized or avoided with counseling (e.g., take with food) or dose reduction.[7]

Prior to treating a patient who reports a drug allergy or intolerance, take a thorough history of the patient's drug reaction. Example questions include: [7]

- Is there any medicine you cannot take for any reason? By what route did you receive the drug?
- Describe the reaction. How was the reaction managed?
- How soon after taking the drug did your reaction occur?
- When the offending drug was stopped, what happened?
- Why was the medication prescribed?
- How long ago did the reaction occur?
- What other medications, including OTCs or supplements, were you taking when the reaction occurred? What foods had you recently eaten that may have caused the reaction?
- Have you since taken the same drug? If so, what happened?
- Have you taken a similar drug since the reaction happened? If so, what happened?
- Have you ever had the same reaction with a different drug?

Identify inactive ingredients in medications – using the following resources:

- DailyMed: Use U.S. product labeling information as a first step to identify inactive ingredients
- U.S. Food & Drug Administration. Inactive Ingredients in Approved Drug Products Search: Frequently Asked Questions. Reviewed January 26, 2022. Site link
- Gluten-specific Resources:
  - Gluten Free Drugs
  - U.S. Food & Drug Administration - Medications and Gluten
  - Beyond Celiac – Gluten in Medications
- Contact the manufacturer when product labeling lacks the specific details needed. Prepare for the inquiry with specific information such as the product NDC number.
- Ask your pharmacist!

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